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ABO blood group does not impact incidence or outcomes of surgery for acute type A aortic dissection

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ABSTRACT

Objectives. To evaluate the distribution and impact of ABO blood groups on postoperative outcomes in patients undergoing surgery for acute type A aortic dissection (ATAAD). **Design.** A total of 1144 surgical ATAAD patients from eight Nordic centres constituting the Nordic consortium for acute type A aortic dissection (NORCAAD) were analysed. Blood group O patients were compared to non-O subjects. The relative frequency of blood groups was assessed with t-distribution, modified for weighted proportions. Multivariable logistic regression was performed to identify independent predictors of 30-day mortality. Cox regression analyses were performed for assessing independent predictors of late mortality. **Results.** There was no significant difference in the proportions of blood group O between the study populations in the NORCAAD registry and the background population (40.6 (95% CI 37.7–43.4)% vs 39.0 (95% CI 39.0–39.0)%). ABO blood group was not associated with any significant change in risk of 30-day or late mortality, with the exception of blood group A being an independent predictor of late mortality. Prevalence of postoperative complications was similar between the ABO blood groups. **Conclusions.** In this large cohort of Nordic ATAAD patients, there were no associations between ABO blood group and surgical incidence or outcomes, including postoperative complications and survival.

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Aorta; aneurysm; dissection; blood group; NORCAAD

Introduction

Acute type A aortic dissection (ATAAD) is associated with numerous risk factors, including hypertension, age, atherosclerosis and smoking [1,2]. It is well-known that different ABO blood groups are associated with altered risks of venous thromboembolism and occlusive arterial disease [3–7], but the impact of blood groups in the setting of ATAAD and associated surgery has not been evaluated.

In a previous study, it was reported that blood group O may be over-represented in patients with abdominal aortic aneurysm [8] but in a more recent study of more than two million Swedish blood donors and recipients of blood transfusions, no certain association was observed between blood group and the incidence of aortic aneurysms or aortic dissection (Zindovic et al. ABO blood group and aortic disease- A nation-wide cohort study. Manuscript in preparation). Additionally, without a clear understanding of the mechanism, it has been reported that blood group AB is

associated with improved long-term survival after cardiac surgery [9,10].

The aim of the present study was to evaluate the distribution of ABO blood groups and their impact on surgical outcomes in a large, well-defined cohort of ATAAD patients from The Nordic Consortium for Acute Type A Aortic Dissection (NORCAAD) database.


Materials and methods

This study was approved by the institutional review board of each participating centre.

Study design

This was a retrospective, multicentre study based on the NORCAAD registry of patients who underwent surgery for ATAAD from 1 January 2005 to 31 December 2014 at eight

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tertiary centres in Denmark, Finland, Iceland, and Sweden. As previously described, 194 clinical variables were collected and up until 2014, a total of 1159 patients were included in the registry [11].

Blood group data

For comparison of blood group distribution, blood groups of the background population were collected from several sources. The distribution of blood groups from Finland was obtained from the Finnish Red Cross Blood Service (www.bloodservice.fi) and national data was used for both of the Finnish sites. The distributions of the population of Iceland were acquired from the Blood Bank of the National University Hospital, Reykjavik, Iceland [12] and information on blood groups from the Swedish and Danish populations were collected from the Scandinavian Donations and Transfusions database (SCANDAT2) [13]. Separate distributions were obtained for the catchment areas of all four Swedish sites, whereas national data was used for the single Danish site. SCANDAT2 data relied on any individuals whose blood group was determined for any cause (e.g. preoperative blood typing, donation of blood or need for transfusion) whereas remaining sources were based on blood donor data.

Definitions and endpoints

Primary endpoints were the proportion of blood group O in the study sample and the association between blood group O with 30-day mortality and late mortality. Outcomes in relation to specific blood groups, as well as postoperative complications were regarded as secondary endpoints.

Acute aortic dissections were defined as those instances in which surgery was performed within 14 days of symptom onset. Malperfusion was defined as end-organ ischemia, branch vessel obstruction or occlusion as described previously [14] and Penn classes were defined as Aa, absence of organ ischemia; Ab, localised ischemia; Ac, generalised ischemia; or Abc, localised and generalised ischemia together. Hypotensive shock was defined as systolic blood pressure < 90 mmHg, regardless of etiology. In-hospital mortality was defined as death during index admission at the operating hospital, 30-day mortality as death within 30 days of surgery and late mortality as all-cause mortality more than 30 days after surgery. Major bleeding was a modified version of the composite variable used in the BART study [15] and defined as one or more of the following: reoperation due to bleeding, chest tube output >1500 mL within the first 12 hours, >10 units (U) of red blood cell transfusions or death due to bleeding. Perioperative MI was defined as postoperative CK-MB >70 µg/l, new Q wave or left bundle branch block on EKG. Postoperative stroke was defined as a permanent neurological injury with or without CT confirmation. Coma was defined as unconsciousness lasting more than 24 hours, not attributable to sedation.

Surgical procedures

As reported in detail elsewhere, median sternotomy, cardiopulmonary bypass, and intermittent cardioplegic arrest were routinely used [11]. The site of cannulation is varied by centre, patient, and surgeon. In most instances, open distal surgical repair was performed including resection and inspection of the aortic arch under deep (<20°C) or moderate (21–30°C) hypothermic circulatory arrest, with or without the use of selective cerebral perfusion. The extent of distal repair depended on the extent of dissection and the location of the intimal tear. Surgery requiring re-implantation of any supra-aortic branches was considered an arch procedure. Aortic valve replacement or total root replacement was performed when necessary and when possible the competence of the aortic valve was restored via subcommissural plication, commissural resuspension, or valvuloplasty. Concomitant procedures (e.g. coronary artery bypass) were performed when required.

Statistical analysis

Categorical data were given as proportions and continuous variables were expressed as mean ± standard deviation (SD). Normally distributed data was presented as mean ± standard deviation (SD) whereas medians and interquartile ranges (IQRs) were reported in skewed distributions. Groups were compared using chi-square test and Mann-Whitney U test. Trends were analysed using Linear-by-Linear association. The proportion of individuals with blood group O in the background population was estimated from the distribution of blood types in the different regions. The proportion for each region was weighted according to the region's contribution to the NORCAAD database providing a weighted proportion for the background population. In turn, the proportion of group O in the background population was compared to the proportion in the NORCAAD database using a confidence interval (CI) based on t-distribution, modified for weighted proportions. Univariable and multivariable logistic regression analyses were performed to evaluate independent predictors of 30-day mortality. Due to the risk of multicollinearity, malperfusion was assessed using only the "any malperfusion" variable. With regard to blood groups, blood group O vs non-O and the individual blood groups (O, A, B, and AB) were analysed in separate models. Remaining variables constituted the baseline model and the model with "blood group O vs non-O" constituted the default analysis. Predictors of late mortality in 30-day survivors were analysed using the Cox proportional hazard regression. Independent predictors remaining at the last steps of each model were re-evaluated using the enter method and the proportional hazards assumptions were verified with adequate diagnostic tools. No adjustments to meet the assumptions were necessary for any variable.

The regression models relied on complete case analysis (98.8% and 98.0% of possible cases in the multivariable logistic regression and Cox regression, respectively) and missing cases are presented in [Supplementary Tables 1 and 2](#). The inclusion criterion for the full regression model was

Table 1. Blood group distributions in the NORCAAD registry and the background populations by country or site, according to which was available.

NORCAAD							
Blood group	Denmark (N = 163)	Finland (N = 124)	Iceland (N = 30)	Gothenburg (N = 242)	Lund (N = 226)	Orebro (N = 100)	Stockholm (N = 261)
O	73 (44.8)	36 (29.0)	17 (56.7)	100 (41.3)	102 (45.1)	32 (32.0)	105 (40.2)
A	69 (42.3)	58 (46.8)	8 (26.7)	105 (43.4)	88 (38.9)	47 (47.0)	124 (47.5)
B	14 (8.6)	21 (16.9)	4 (13.3)	23 (9.5)	27 (11.9)	17 (17.0)	24 (9.2)
AB	7 (4.3)	9 (7.3)	1 (3.3)	14 (5.8)	9 (4.0)	4 (4.0)	8 (3.1)
Background population							
Blood group	Denmark (N = 988705)	Finland (N = 80880)	Iceland (N = 7528)	Gothenburg (N = 536229)	Lund (N = 511562)	Orebro (N = 129257)	Stockholm (N = 755216)
O	416581 (42.1)	27141 (33.6)	4316 (57.3)	209200 (39.0)	201982 (39.5)	47665 (36.9)	285227 (37.8)
A	419228 (42.4)	33413 (41.3)	2347 (31.2)	238974 (44.6)	225189 (44.0)	59499 (46.0)	333234 (44.1)
B	107393 (10.9)	13792 (17.0)	662 (8.8)	61806 (11.5)	59553 (11.6)	15079 (11.7)	95825 (12.7)
AB	45503 (4.6)	6534 (8.1)	199 (2.6)	26249 (4.9)	24838 (4.9)	7014 (5.4)	40930 (5.4)

Values are expressed as number (percentage).

$p \leq .100$ and the limit for stepwise backward elimination was $p \leq .100$. Statistically significant variables ($p < .05$) at the last step were re-evaluated using the enter method. Blood group variables were forced into the models. The results of the logistic regression analyses were expressed as odds ratios (ORs) and those of the Cox regression analysis as hazard ratios (HRs), both with 95% confidence intervals (CIs). Any p -value $< .05$ was considered statistically significant. Statistical analysis relied on standard software (IBM SPSS Statistics for Mac, version 24.0, released 2016; IBM Corp., Armonk, NY).

Results

Study population and follow-up

Up until December 2014, a total of 1,159 patients were included in the NORCAAD registry. ABO blood group was available for 1146 patients, who constituted the study population. Follow-up of the study cohort, performed in January 2015, was 98.1% complete with a mean follow-up time of 3.1 ± 2.9 years.

Blood group distribution

The ABO blood group distributions in the NORCAAD database and the background population are presented in Table 1. There was no significant difference in the proportions of blood group O between the study populations. In the NORCAAD registry, 40.6% of the patients had blood group O with an estimated 95% CI of 37.7–43.4% and in the background population, 39.0 (95% CI 39.0–39.0)% were blood group O patients.

Baseline and surgical characteristics

Baseline data and surgical characteristics for the study population were similar between blood group O and non-O patients (Table 2). Data specific for each blood group is presented in Supplementary Table 3.

Table 2. Baseline and surgical characteristics of the study population, stratified per blood group O and non-blood group O patients.

Characteristic	Non-O (N = 681)	O (N = 465)	<i>p</i>
Age	61.7 ± 12.1	61.3 ± 12.2	.571
Male gender	453 (66.5)	322 (69.2)	.333
Hypertension	370 (54.3)	226 (48.6)	.057
History of aortic aneurysm	66 (9.7)	42 (9.0)	.708
Connective tissue disease	29 (4.3)	25 (5.4)	.381
Diabetes mellitus	15 (2.2)	11 (2.4)	.856
History of stroke	22 (3.2)	23 (4.9)	.142
Chronic kidney disease	11 (1.6)	10 (2.2)	.507
COPD	39 (5.7)	29 (6.2)	.720
DeBakey type 1	502 (73.7)	341 (73.3)	.886
Intramural hematoma	54 (7.9)	37 (8.0)	.987
Hypotensive shock	146 (21.4)	87 (18.7)	.260
Cardiac arrest	37 (5.4)	20 (4.3)	.387
Malperfusion	231 (33.9)	147 (31.6)	.415
Cardiac malperfusion	55 (9.0)	39 (9.0)	.995
Cerebral malperfusion	51 (8.4)	38 (9.1)	.718
Renal malperfusion	44 (7.3)	20 (4.8)	.105
Gastrointestinal malperfusion	20 (3.3)	15 (3.6)	.811
Peripheral malperfusion	132 (21.9)	71 (17.0)	.053
Penn Class			.982
Aa	367 (53.9)	254 (54.6)	
Ab	165 (24.2)	105 (22.6)	
Ac	112 (16.4)	81 (17.4)	
Abc	37 (5.4)	25 (5.4)	
Proximal surgical technique			.479
Supracoronary graft	472 (69.3)	331 (71.2)	
Supracoronary graft + AVR	20 (2.9)	12 (2.6)	
Bentall procedure	160 (23.5)	106 (22.8)	
Distal surgical technique			.829
Ascending aorta	479 (71.6)	330 (71.3)	
Hemiarch procedure	140 (20.9)	104 (22.5)	
Arch procedure	41 (6.1)	24 (5.2)	
CPB time, min	194 (155–241)	188 (157–230)	.258
Cross-clamp time, min	95 (68–134)	88 (63–126)	.077
HCA time, min	27 (20–36)	26 (20–34)	.252
Lowest core temperature, °C	19.9 (18–24)	19 (18–24)	.413

Values are expressed as number (percentage), as median (interquartile range (IQR), or mean ± standard deviation (SD).

COPD: chronic obstructive pulmonary disease; AVR: aortic valve replacement; CPB: cardiopulmonary bypass; HCA: hypothermic circulatory arrest.

Mortality and postoperative complications

Blood group O patients had significantly lower intraoperative mortality than did non-O patients (5.4% vs 8.7%, $p = .036$), whereas 30-day mortality was similar between the groups (17.2% vs 17.7%, $p = .829$). In multivariable

Table 3. Early mortality and postoperative complications in the population, presented per blood group O and non-blood group O patients.

Characteristic	Non-O (N = 681)	O (N = 465)	p
Intraoperative mortality	59 (8.7)	25 (5.4)	.036
30-day mortality	120 (17.7)	80 (17.2)	.829
In-hospital mortality	110 (16.2)	74 (15.9)	.889
Major bleeding	275 (40.4)	173 (37.2)	.279
Reoperation for bleeding	144 (21.8)	85 (18.7)	.203
Perioperative MI	41 (6.2)	30 (6.6)	.795
Postoperative stroke	108 (16.4)	68 (14.8)	.487
Postoperative coma	59 (9.9)	45 (11.1)	.517
RRT	83 (12.6)	46 (10.1)	.204
Mesenteric ischemia	31 (5.2)	23 (5.7)	.745
DSWI	23 (3.5)	3 (0.7)	.002
Acute limb ischemia	30 (4.6)	13 (2.9)	.147
Ventilatory support >48 h	221 (34.1)	131 (29.0)	.076
Cardiac tamponade	93 (14.1)	65 (14.3)	.927
Postoperative CKMB	25 (15–46)	26 (15–43)	.809
Postoperative Lactate	3.0 (2.1–4.3)	2.9 (2.1–4.3)	.156
Length of stay in ICU, days	4 (2–7)	3 (2–7)	.329

Values are expressed as number (percentage), or as median (IQR).

MI: myocardial infarction; RRT: renal replacement therapy; DSWI: deep sternal wound infection; ICU: intensive care unit.

Table 4. Independent predictors of 30-day mortality.

Characteristic	OR (95% CI)	p
Diabetes mellitus	3.929 (1.499–10.299)	.005
COPD	2.705 (1.446–5.060)	.002
Cardiac arrest	3.368 (1.803–6.290)	<.001
Malperfusion	2.759 (1.936–3.933)	<.001
CPB-time, min	1.007 (1.005–1.009)	<.001
Blood group O (vs Non-O)	1.030 (0.720–1.473)	.871
Blood group		
O	ref.	
A	1.105 (0.757–1.613)	.606
B	0.743 (0.400–1.378)	.346
AB	0.447 (0.154–1.302)	.140

Values are expressed as Odds ratios (OR:s) and 95% Confidence intervals (CI).

COPD: chronic obstructive pulmonary disease.

Table 5. Independent predictors of late mortality in 30-day survivors.

Characteristic	HR (95% CI)	p
Age	1.061 (1.041–1.081)	<.001
Chronic kidney disease	2.997 (1.300–6.907)	.010
COPD	1.837 (1.025–3.292)	.041
Blood group O (vs Non-O)	0.686 (0.465–1.012)	.058
Blood group		
O	ref.	
A	1.543 (1.027–2.319)	.037
B	1.056 (0.549–2.029)	.871
AB	1.720 (0.765–3.866)	.190

Values are expressed as Hazard ratios (HR:s) and 95% Confidence intervals (CI).

COPD: chronic obstructive pulmonary disease.

regression analysis, blood group O was not identified as an independent predictor of 30-day mortality [OR 1.030 (0.720–1.473), $p = .871$] (Tables 3–4; Supplementary Table 5). There were no differences between groups in frequency of major bleeding (37.2% vs 40.4%, $p = .279$) or reoperation for bleeding (18.7% vs 21.8%, $p = .203$). Apart from blood group O patients having a significantly lower occurrence of postoperative deep sternal wound infections (0.7% vs 3.5%, $p = .002$), the rates of other major postoperative complications were similar between the groups. Data per specific blood group is presented in Supplementary Table 4.

In 30-day survivors, there was a non-significant trend towards blood group O having a protective effect on late mortality [HR 0.686 (0.465–1.012), $p = .058$] (Table 5; Supplementary Table 6) and blood group A was identified as an independent predictor of late mortality [HR 1.543 (1.027–2.319), $p = .037$].

Discussion

The present study, which is, to our knowledge, the first to analyse the impact of ABO blood group in surgically treated ATAAD patients, could not demonstrate any association between ABO blood groups and the risk of undergoing ATAAD surgery or surgical outcomes.

ABO blood group antigens are expressed by erythrocytes, as well as by endothelial cells, and, like other surface carbohydrate molecules, may have roles in cell membrane integrity and cell adhesion [16–18]. Glycosylation of the aortic wall plays a key role in normal vascular biology and alterations in glycosylation of the vascular endothelium have been identified as a risk factor for the development of cardiovascular disease [19]. Recently, Avdic *et al.* speculated that glycosylated cross-links rendered the aortic wall more resilient to dilatation and dissection, which could explain a 25% risk reduction for the development of aortic aneurysms and a 47% reduction of risk of aortic dissection in patients with diabetes mellitus type II [20]. In a previous study, Fatic *et al.* demonstrated that blood group O was more common in patients with AAA as compared with a sample from the background population [8]. By contrast, a recent epidemiological study of more than two million Swedish citizens showed no certain association between blood groups and aortic disease, with an incidence risk ratio for aortic dissection of 0.89 (95% CI 0.78–1.01) in non-O donors compared with blood group O donors (Zindovic *et al.* ABO blood group and aortic disease- A nation-wide cohort study. Manuscript in preparation). Considering the results of the current report, it is likely that the glycosylation patterns of N-acetylgalactosamine and D-galactose, the determinants of ABO blood group, do not have a significant effect on the strength of the aortic wall and thus do not influence the risk of aortic dissection in the general population.

It has been reported that up to 49% of patients with ATAAD die prior to reaching the hospital [21], with the first 24 hours after symptom onset being associated with significant mortality and defined as a “hyperacute” state by Booher *et al.* [22]. Preoperative malperfusion is associated with increased mortality in ATAAD patients [14], while bleeding, cardiac failure, and stroke have been identified as the leading causes of in-hospital deaths [23,24]. Since it has been demonstrated that blood group O patients are at a lower risk for both venous and arterial thromboembolism, including myocardial infarction and cerebrovascular stroke [3], it could be speculated that this would have an impact on mortality after ATAAD surgery. The current study showed that blood group O patients were at a lower risk for intraoperative mortality in univariable analysis, however, in

a multivariable model, ABO blood group did not predict 30-day mortality in surgical ATAAD patients.

Bleeding complications after surgery for ATAAD are associated with impaired survival and higher rates of postoperative complications [25,26]. Compared to patients with non-O blood group, blood group O individuals have been shown to have 25–30% lower levels of von Willebrand factor [27]. In theory, this could put them at higher risk of bleeding in association with ATAAD surgery. However, the present study could not demonstrate that blood group O patients were at higher risk of bleeding complications, which is in accordance with a previous report by Welsby et al. showing no association between blood groups and bleeding in 877 patients that underwent coronary artery bypass surgery [9].

Previously, Welsby et al. demonstrated blood group AB patients to be at lower risk of long-term mortality after routine cardiac surgery [10]. In contrast, our results showed a trend towards non-O blood groups being associated with impaired late survival, driven by blood group A, being an independent predictor of late mortality (1.543 (1.027–2.319), $p = .037$). This trend could be explained by non-O patients being generally at an increased risk of cardiovascular and thromboembolic disease [3]. After undergoing surgery, patients with ATAAD enter a chronic state, potentially influenced by surgical complications, malperfusion injuries and false lumen patency. Possibly, the difference between the two studies could be explained by thromboembolic mechanisms having a larger impact on survival in patients with aortic dissection when compared to those undergoing routine procedures. Yet, in the short term, blood groups were not associated with altered rates of postoperative cardiovascular or thromboembolic complications.

The NORCAAD registry is one of the largest databases on ATAAD and, as such, it has provided us the opportunity to perform our analyses in a large and relatively homogeneous study sample. However, the risk of type II errors cannot not be ruled out, but any differences between the groups not detected by this study are most likely of minor clinical importance. The multi-centre nature of the registry has limited the possibility of additional review of patient charts and exposes the inherent shortcomings of a retrospective database. The proportions of ABO blood groups were compared to the background population, partly represented by blood donors from Finland and Iceland. Blood donors tend to be younger and healthier than ATAAD patients, but it has previously been shown that there is no difference in the frequency of blood group O between blood donors and significantly older and co-morbid recipients of blood transfusions from the general population (Zindovic et al. ABO blood group and aortic disease- A nation-wide cohort study. Manuscript in preparation). Therefore, we believe that the blood group distributions of the background populations of these countries are adequately reflected by the distribution of blood groups in blood donors. We do not have full data on causes of death and we cannot, therefore, assess the causality between ATAAD and late mortality. Furthermore, despite the large study sample, we cannot

exclude that some of our analyses were under-powered. Nevertheless, it is our opinion that the size and multi-centre nature of the NORCAAD registry represents the true strength of the current study.

Conclusion

The present study could not demonstrate any association between ABO blood groups and the risk of undergoing surgery for ATAAD. Furthermore, ABO blood groups did not have any impact on rates of postoperative complications or mortality after surgery for ATAAD.

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Disclosure statement

No potential conflict of interest was reported by the authors.

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